A. Claim Amendments

Claim 2 has been amended to specify that the nucleic acid molecule of the claim is one that encodes a chimeric TNFα polypeptide that is more resistant to cell membrane cleavage into soluble TNFα than are native TNFα and TNFα lacking the metalloproteinase cleavage site present from the valine 77 to the proline 88 of native TNFα. Claims 71 through 74 are newly added, and are drawn to the nucleic acid molecules of Claim 2, wherein the resistance to cleavage of the encoded chimeric TNFα polypeptide is about 90% greater than that of the reference polypeptides.

Support for the claim amendment and for the newly added claims is found in the Specification at paragraphs 0007, 0009 and 0078, and is exemplified by the data shown in, for example, Figure 5. No new matter has been added to the application by the amendment and newly added claims, entry of which is therefore respectfully requested.

B. Response to Rejection under 35 USC Section 102(a)

Claims 2-4, 8, 11-12, 27-29, 32-41 and 68-75 are rejected as being anticipated by Cantwell, et al. The Office Action describes Cantwell as teaching "generating chimeric TNF genes encoding the receptor-binding domain of TNF lacking the known site(s) for cleavage by matrix metalloproteinases splied onto transmembrane domains of other members of the TNF family, including CD154." (Action at page 3). Applicants respectfully disagree.

As explained in the enclosed Supplemental Declaration of Dr. Charles Prussak[1] (an inventor and a co-author of Cantwell), the CD154-TNF molecule described had an ***intact*** Domain III. The only molecule referred to in Cantwell that included a modified Domain III element is the non-chimeric ΔTNF molecule, from which a metalloproteinase (mmp) cleavage site was removed. Thus, Cantwell neither teaches nor suggests a chimeric molecule from which a portion of the

[1] The Declaration was originally submitted in a granted EU counterpart application.

Domain III element has been deleted (i.e., an mmp cleavage site, in some cases extending from Domain III into Domain IV), has been removed.

Reconsideration and withdrawal of the rejection under Section 102 based on Cantwell, et al. is therefore respectfully requested.

C. Response to Rejection of Claims 2-4, 8, 11-12, 27-29, 32-41 and 68-75 under 35 USC Section 103(a)

The claims stand rejected as obvious over Kipps, *et al.* US Patent No. 7,070,771 (and/or the same disclosure of Kipps, *et al.*, WO 98/26061), in view of Mueller, *et al.*, *J.Biol.Chem.*, 274:38112-38118, 1999.

As discussed in the prior amendment, Mueller, et al. teaches a full-length TNFα molecule from which a portion of the wild-type Domain III was removed; i.e., the portion from valine 77 to proline 88 (the molecule so produced is hereafter referred to as Δmmp-TNFα). Cells expressing TNFα from Δmmp-TNFα did so more stably, but soluble TNFα (sTNFα) could still be found at significant levels in the cell supernatants (see, e.g., Figure 2B, lane 5, at Mueller, *et al.*, page 38114, and Specification at paragraph 007).

In the Office Action, the Examiner responds that Mueller, *et al.* did produce a functional TNF molecule that was, "for the most part," membrane stabilized, at least in certain cell lines (citing to the Foon Declaration, at paragraph 5). However, as now emphasized in the claims and established in the Specification (see, e.g., Figure 5), the molecules of the invention produce a chimeric TNFα that is magnitudes of order more resistant to cleavage than the molecule described by Mueller, *et al.* (lacking the mmp cleavage site between Val77 and Pro88 of TNFα; i.e., Δ TNFα).

Mueller, *et al.* alludes to the presence of other mmp cleavage sites in TNFα as being potentially responsible for the persistent production of sTNFα from their ΔTNFα mutant, but offer no guidance as to the location of such other putative sites nor, more to the point, any suggestion as to how the persistent secretion from ΔTNFα might be overcome (Mueller, *et al.,* page 38117, top left column). Thus, Mueller, *et al.* itself does not point the art to TNFα molecules whose enhanced resistance to cleavage is provided *not* by removing an mmp cleavage site from Domain III of TNFα (per Mueller), but by removing it from Domain III of CD154 *and* replacing the cleavage site in TNFα therewith (per the invention)[2].

Kipps, *et al.* is similarly lacking in guidance, in that nothing in the reference points the art to means for resisting cleavage of TNFα. Instead, the focus of the reference is on providing molecules that are capable of expression in cells in which expression might otherwise be lacking; e.g., for antigen presentation of the disclosed chimera (see, e.g., Col. 3, line 66 to Col. 4, line 19). Kipps, et al.. does suggest a wide variety of TNF family chimera, including ones containing one or more domains from the CD154 and TNFα molecules; however, the only passage of relevance to reducing sTNFα production is the description of Figure 28, which identifies known mmp cleavage sites. Thus, with respect to resistance to secretion of TNFα, Kipps, *et al.* does not provide guidance beyond that previously provided by Mueller, *et al.*

Taken together, therefore, Kipps, et al. and Mueller, et al. can at most be read to suggest the concept that removing mmp cleavage sites from a TNFα molecule (possibly including a chimeric molecule) might reduce sTNFα production to the limited degree observed by Mueller, *et al.* However, nothing in the references would lead one to suspect that the replacement of Domain III of TNFα with a CD154 domain fragment that itself lacks an mmp cleavage site would enhance

[2] Notably, the molecules of the invention further differ from the Δ TNFα of Mueller, et al., in that the former are not cell type specific (Specification at 0111 and Figure 5), lending the invention greater potential utility than the molecules described by Mueller, et al. (Foon Declaration, at paragraph 7).

the chimera's resistance to cleavage into sTNFα to a much greater degree than observed by Mueller, *et al.* for Δ TNFα.

The Office Action asserts that the addition of the Kornbluth reference to the cited combination provides the art with motivation to make chimeric molecules in which the CD154 element lacks a mmp cleavage site. Applicants respectfully disagree.

It is axiomatic that, for purposes of evaluating a reference under Section 103, *inter alia*, its teachings must be viewed as a whole. The principal focus of the Kornbluth reference is on the creation of soluble fusion proteins (see, paragraphs 0002, 0009, 0013 and 0094-0096). The fusion protein of the invention is one in which the mmp cleavage sites of the CD154 membrane element are intact (paragraph 0098). The only reference to changing the solubility profile of the fusion protein in Kornbluth is at paragraph 0098, where it is suggested that mutagenesis of the CD154 cleavage sites might *delay* release of the soluble protein from cells.

Therefore, nothing in Kornbluth suggests that removal of the mmp cleavage site from the CD154 molecule would prevent release of an otherwise soluble CD154 fusion protein to any extent, much less the extent achieved in the present invention. To the contrary, modifying the CD154 portion of the Kornbluth molecule to prevent release of the soluble protein would defeat the purpose of the Kornbluth invention; i.e., to provide soluble CD154-SPD fusion proteins. Therefore, Kornbluth cannot be fairly read to suggest that elimination of soluble CD154 protein release could be achieved.

Further, it must be appreciated that Kornbluth's teachings are, by their explicit terms, limited to the CD154-SPD fusion proteins contemplated. No extrapolation of Kornbluth can be made to other CD154 fusion proteins. As stated in Kornbluth:

> "Accordingly, it would be expected that *collectins other than SPD might confer different cell-binding and pharmacokinetic behaviors upon a fusion protein.* For example, macrophages are known to take up and degrade whole SPD***...filf a fusion protein other than SPD were used, the disposition of the fusion protein might be altered.***"
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> Paragraph 0098 (emphasis added).

Therefore, taken in view of Mueller, *et al.* and Kipps, *et al.*, Kornbluth provides no reason to believe that CD154 chimera would have greater resistance to cleavage than any other TNF family ligand chimera. To the contrary, Kornbluth provides reason to believe that the properties that CD154 chimera other than CD154-SPD might possess are unpredictable.

Even if one were to experiment with removing mmp cleavage sites from different chimera, the effort would involve the daunting task of identifying and eliminating an array of mmp cleavage site from as many as the 162 different chimeric species disclosed by Kipps, *et al.* Moreover, the task would be performed without any reason to expect that the particular species now claimed would provide near elimination, not just reduction, of sTNFα release. Thus, the inventors' discovery of the presently claimed molecules—ones with better resistance to cleavage than either native TNFα or ΔTNFα—could not have been predicted.

According to *KSR Int'l Co. v. Teleflex, Inc.*, 550 US __, 2007 WL 123837, at 12 (2007), "[t]he combination of familiar elements according to known methods is likely to be obvious *when it does no more than yield predictable results.*" (Emphasis added). Here, Applicants submit that one could construct a wide range of different constructs following Kipps, *et al.* (to obtain expression in expression-incompetent cell types), and might try to modify cleavage sites in the chimera (to enhance stability). If one did so, one might possibly hope that release of soluble TNFa could be reduced from molecules lacking a cleavage site from Domain III of the TNFa molecule and/or that the chimera might be expressible in otherwise expression-incompetent cell types. The invention, however, yields much more--a CD154 (Domain III)-TNFa (Domain IV)

chimera lacking a cleavage site in Domain III of the CD154 element from which soluble TNFa release from transfected cells is virtually eliminated.

Therefore, even with the addition of Kornbluth, the cited references would not readily lead one of ordinary skill in the art to predict that soluble TNFa release could be eliminated from cells transfected with the claimed chimera. In corroboration of that conclusion, enclosed is the Declaration of Dr. Kenneth A. Foon, now a Professor of Medicine at the University of Pittsburgh. After detailed consideration of the cited references, Dr. Foon concludes:

> Nothing in the references points one to select a CD154/TNFα chimera lacking a metalloproteinase site in particular, nor do the references offer a reasonable basis upon which to expect that cleavage from such a chimera would be abrogated to the same or greater degree than demonstrated by Mueller, et al. for the TNF molecule they tested. Even in view of the Kipps application's disclosure, ***one could not have predicted, a priori, the best combination of TNF family member segments to fuse to the domain IV of TNF to create a stabilized molecule.***
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> Foon Declaration, paragraph 7 (emphasis added).

Based on all of the foregoing, as well as the Declaration of Dr. Prussak submitted with the Amendment of October 5, 2006, Applicants respectfully submit that the invention of the pending claims is not obvious over Kipps, *et al.*, in view of Mueller, *et al.* Reconsideration and withdrawal of the claims rejection under 35 USC §103 is therefore requested.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge $230.00 as payment for the Petition for Two-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: January 17, 2008

Stacy L. Taylor
Registration No. 34,842
Telephone: (858) 677-1423
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213